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ORIGINAL ARTICLE

Scintigraphic detection of TNF-driven inflammation by radiolabelled certolizumab pegol in patients with rheumatoid arthritis and spondyloarthritis

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ABSTRACT

Background: Biologicals are the cornerstone for many treatment algorithms in inflammatory arthritis. While tumour necrosis factor (TNF) inhibitors may achieve important responses in ~50% of patients with rheumatoid arthritis (RA) and spondyloarthritis (SpA), a significant fraction of patients are partial or non-responders. We hypothesised that in vivo assessment of TNF by scintigraphy with ^{99m}Tc-radiolabelled certolizumab pegol (CZP) might lead to a more 'evidence-based biological therapy'.

Objectives: Our goal was to perform a proof-of-concept study of in vivo detection of TNF by immunoscintigraphy of a radiolabelled TNF inhibitor in RA and SpA, and correlate this with clinical, imaging findings and therapeutic outcome.

Methods: CZP was conjugated with succinimidyl-6-hydrazino-nicotinamide and subsequently radiolabelled with Tc^{99m}. Whole body and static images of hands, feet and sacroiliac joints of 20 patients (5 RA; 15 SpA) were acquired at 3 time points. Immunoscintigraphic findings were scored semiquantitatively. Subsequently, all patients were treated with CZP.

Results: In peripheral joints, clinically affected joints or abnormal ultrasound findings were observed more frequently ($p < 0.001$) in the scintigraphic-positive group. In patients with axial SpA, bone marrow edema on MRI was detected more frequently ($p < 0.001$) in quadrants with tracer uptake. At the patient level, the odds of a joint remaining tender despite 24 weeks of CZP treatment was significantly smaller in joints with clear tracer uptake as compared with those with no uptake (OR=0.42, $p=0.04$).

Conclusions: Immunoscintigraphy with radiolabelled CZP demonstrated both axial and peripheral inflammation, and displayed good correlation with clinical features, conventional imaging and therapy response.

Trial registration number: NCT01590966; Results.

Key messages

- Typical joint involvement patterns in peripheral and axial disease were detected by using a immunoscintigraphic procedure with radiolabelled certolizumab pegol (CZP): polyarticular pattern in rheumatoid arthritis, distal interphalangeal joint (DIP) involvement and dactylitis in psoriatic arthritis, and enthesitis and sacroiliitis in spondyloarthritis (SpA).
- A strong relationship with clinical involvement and immunoscintigraphic uptake was observed; tender or swollen joints or abnormal ultrasound findings were significantly more prevalent when scintigraphy was positive.
- In patients with axial SpA, bone marrow edema on MRI was observed more frequently in quadrants that also showed uptake of the radiolabelled CZP.
- A marked relationship with therapy response was observed: the odds of a joint remaining tender despite 24 weeks of CZP treatment was significantly smaller in joints with clear tracer uptake as compared to those without.

INTRODUCTION

Rheumatoid arthritis (RA) and spondyloarthritis (SpA) are both chronic inflammatory joint diseases, with a combined prevalence close to 2%. If untreated, persistent inflammation may lead to functional disability, progressive structural damage and potentially to also a number of extra-articular manifestations or comorbidities.^{1 2} Currently, the aetiology is unknown, but a combination of predisposing genetic factors, and person-related or environmental factors (age, gender, infectious agents, smoking, dietary factors) is suspected to play a role in disease

pathogenesis.^{3 4} Treatment strategies for SpA and RA have changed dramatically over the last decade mainly as a consequence of our growing knowledge of the pathogenetic role of proinflammatory cytokines, such as tumour necrosis factor α (TNF- α).^{5 6}

Immunohistological studies demonstrated the presence of TNF- α and its receptors in inflamed tissues of peripheral joints and/or sacroiliac joints (SIJs).⁷ The introduction of 'biological agents' targeting TNF- α , with either monoclonal antibodies (including Fab fragments) or receptor-fusion proteins, has revolutionised our therapeutic armamentarium. Treatments neutralising TNF- α have the longest track record in RA and SpA; currently four monoclonal antibodies (adalimumab, certolizumab, golimumab, infliximab) and one receptor-fusion protein (etanercept) are available.⁸ Certolizumab pegol (CZP; UCB Celltech, Slough, Berkshire, UK) is an engineered humanised monoclonal antibody Fc-free Fab' fragment with specificity for human TNF- α , manufactured in *Escherichia coli*. The antibody fragment is subsequently purified and conjugated with high molecular weight polyethylene glycol (PEG; 40 kDa). CZP is approved worldwide for adult patients with moderate-to-severe active RA, ankylosing spondylitis (AS) and psoriatic arthritis;^{9–11} moreover, the drug also received marketing authorisation in Europe for the indication of non-radiographic axial SpA (axSpA).¹² In addition to RA, CZP has demonstrated a positive benefit risk in Crohn's disease and psoriasis.^{13 14}

In clinical trials for RA and SpA, ~50% of patients achieve a clinically important response such as an American College of Rheumatology (ACR) 50% response rate or the Assessment of SpondyloArthritis international Society (ASAS) 40% response rate.^{9 11 15–22} Despite an overall impressive improvement in clinical signs and symptoms when a TNF-blocking agent is administered, there is still a significant proportion of patients who do not reach a relevant response (primary non-responder), have insufficient improvement, or who lose an initial good response over time (secondary non-responder). This may be due to lower levels of TNF- α expression at the site of inflammation as it is known that there may be a large interindividual and intraindividual variability in these levels,²³ or to the fact that the disease is in fact predominantly driven by other proinflammatory cytokines. In an era of evidence-based medicine, it is disappointing to realise that treatment decisions or strategies, even for expensive biological agents, are driven by patient-reported outcomes, the difficult to standardise clinical examinations (joint counts), rather aspecific laboratory parameters (elevated C reactive protein (CRP)) or questionable imaging cut-offs (erosions, sacroiliitis grade 2 by modified New York criteria for AS). An accurate way of predicting a relevant clinical response to a certain targeted treatment would allow for a better patient selection. Molecular imaging studies aiming at selectively visualising TNF- α (or another suspected culprit cytokine) in vivo at the site of clinical inflammation could be an

attractive alternative to other less specific and/or invasive techniques such as bone scintigraphy with 99mTc-labelled diphosphonates or synovial biopsies taken by arthroscopic procedures. This more rational approach of determining the most appropriate biological treatment for an individual patient may also have relevant consequences for the cost-efficacy of our currently available biological drugs, and even have an impact on the design of future clinical trials with targeted therapies. Therefore, we performed a proof-of-concept study to explore the possibility of visualising TNF-driven disease in patients with active RA and SpA using scintigraphy with Tc99m-labelled CZP as tracer, and to correlate the anti-TNF bound tracer with the localisation of active clinical inflammation.

PATIENTS AND METHODS

Patients

The study was approved by the Medical Ethics Committee of the Ghent University Hospital, and each patient gave written informed consent. The study was conducted in compliance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. (EudraCT number: 2009-017998-37).

We included 20 adult (18–70 years) patients with RA (n=5), peripheral SpA (pSpA; n=6) or axSpA (n=9). Patients were recruited from the Rheumatology Outpatient Clinic of the University of Ghent, Belgium, from November 2012 until November 2013.

All patients with RA fulfilled both the ACR revised criteria for the diagnosis of RA²⁴ and the 2010 ACR/European League Against Rheumatism (EULAR) classification criteria,²⁵ and all patients with SpA fulfilled the current ASAS classification criteria for axSpA or pSpA.^{26 27} Patients with RA fulfilled Belgian reimbursement criteria for the initiation of anti-TNF agents (including failure of at least two disease-modifying antirheumatic drugs, one of these being methotrexate) and had active disease Disease Activity Score in 28 joints (DAS28 \geq 3.7) with at least five swollen joints at screening. Patients with pSpA had active arthritis, dactylitis or enthesitis at screening despite treatment with an adequate stable dose of sulfasalazine or methotrexate for at least 3 months, or a stable, full dose of non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks. Patients with axSpA were required to still have active disease (despite a stable, full dose of NSAIDs for at least 4 weeks), defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) \geq 4 (0–10) and active inflammatory lesions on MRI of the SIJs (according to the definition of a positive MRI proposed by the ASAS consortium) or radiographic sacroiliitis according to the modified New York criteria.²⁶ Prior treatment with any biological treatment was an exclusion criterion. All patients were screened for latent tuberculosis by means of a tuberculin skin test and chest X-ray.

Clinical and laboratory assessments

Patients were evaluated through screening at baseline (prior to the CZP scintigraphy), prior to initiation of CZP, and at weeks 12 and 24 after start of CZP. Evaluations were performed by the same rheumatologist (PC) and consisted of a full rheumatological examination, including a 66/68 joint count, enthesitis and dactylitis assessments as well as an evaluation of axial metrology. At all visits, a number of patient-reported outcomes was assessed, including patient global assessment (PGA) of disease activity, PGA of pain and Short Form (SF)-36 for all patients, BASDAI and Bath Ankylosing Spondylitis Functional Index (BASFI) for patients with axSpA, and the Health Assessment Questionnaire (HAQ) for patients with RA. During the screening 12 and 24 weeks after treatment, routine blood samples were taken to assess potential toxicity of CZP treatment, and determine erythrocyte sedimentation rate (normal level <20 mm/hour) and level of CRP (normal level <5 mg/L). This allowed for the calculation of validated composite disease activity scores such as the DAS28 for RA, and the Ankylosing Spondylitis Disease Activity Score (ASDAS) for patients with SpA.

Imaging assessments

Ultrasound examination

Ultrasound (US) evaluation was performed at baseline and after 12 weeks treatment with CZP in patients with RA and pSpA. Systematic multiplanar grey scale (GS) and power Doppler (PD) examinations were carried out with an ESAOTE MyLab60 using multifrequency linear transducers (6–18 MHz). PD imaging was performed by selecting a region of interest that included the bony margins, articular space and a variable view of surrounding tissues (depending on the joint size). PD variables were adjusted to the lowest permissible pulse repetition frequency (PRF) to maximise sensitivity. This setting resulted in a PRF between 500 and 1000 Hz depending on the joint scanned. Low wall filters were used. Colour gain was set just below the level at which colour noise appeared on the underlying bone (no flow should be visualised at the bony surface). We evaluated both wrists, ankles and subtalar joints, as well as all metacarpophalangeal (MCP) and metatarsophalangeal joints. Synovitis and tenosynovitis were assessed according to the EULAR criteria²⁸ and the OMERACT definition.²⁹ Synovitis and synovial and tenosynovial vascularity were scored semiquantitatively (grade 0–3) by PD US according to Szkudlarek *et al.*³⁰ Synovitis (effusion and synovial hypertrophy combined) in GS US was analysed semiquantitatively as described by Scheel *et al.*³¹ Tenosynovitis in GS US was registered as being absent (0) or present (1).

MRI

All patients with axSpA and one patient with pSpA underwent MRI of the SIJs. Images were obtained on a 1.5 T MRI unit (Avanto/Symphony, Siemens Medical, Erlangen, Germany). The SIJs were imaged in a body

flexed array coil (Siemens Medical, Erlangen, Germany). The sequence protocol included semicoronal (along long axis of the sacral bone) T1-weighted turbo spin echo (slice thickness (ST) 3 mm; repetition time/echo time (TR/TE) 595/20 ms), semicoronal short tau inversion recovery (STIR) (ST 3 mm; TR/TE/inversion time (TI) 5030/67/150 ms) and axial STIR (ST 5 mm; TR/TE/TI 7540/67/150 ms). Sacroiliitis on MRI was scored positive or negative according to the definition proposed by the ASAS consortium.²⁶ Each SIJ was divided into four quadrants and evaluated on eight coronal 3 mm MRI slices. Bone marrow edema (BME) was scored per quadrant as either absent or present (on two consecutive slices), thus providing a total score between 0 and 8. BME of the SIJs was also scored using the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system by certified readers for the SPARCC scoring system.³² The presence of an intense signal (comparable to blood vessels) or depth ≥ 1 cm anywhere within each SIJ of the six slices is given an additional score (0=absent/1=present). Since in our centre 3 mm slices are used, eight slices were evaluated and converted to a maximum score of 72. MRI of the SIJs was performed within the week before the immunoscintigraphy was obtained.

Scintigraphic assessments

Radiolabelling procedure of CZP

Lyophilised CZP was reconstituted with water for injection, filtered and dialysed, and subsequently incubated with succinimidyl-6-hydrazino-nicotinamide (S-HYNIC, ABX GmbH, Radeberg, Germany). After removal of the unreacted S-HYNIC, a bifunctional crosslinker, the solution was diluted with acetate buffer to a pH of 5 and filtered through a 0.22 μ m membrane filter. Solutions of 1.25 mg S-HYNIC CZP were dispensed in 1.0 mL glass vials stored at -80°C .

For the radiolabelling procedure, a co-ligand kit consisting of a tin(II) sulfate (4.66 mM, Sigma Aldrich, Steinheim, Germany) and tricine (55.81 mM, Sigma Aldrich) diluted solution (50 μ L) was added to the S-HYNIC CZP vial. Subsequently, 925 MBq ($\pm 10\%$) freshly eluted Tc99m pertechnetate was added to this vial. This was incubated for 15 min at room temperature. Finally, physiological saline was added to dilute the radiopharmaceutical formulation in a total volume of 3 mL. All handling was performed under aseptic conditions. Quality control was carried out by instant thin layer chromatography with Silica gel (SilG) as stationary phase and 0.9% NaCl solution as mobile phase. For clinical use, the radiochemical yield needed to exceed 90%.

Scintigraphic procedure

Patients were injected intravenously with ~ 740 MBq Tc99m-labelled CZP (10.6 MBq/kg). All patients were scanned on the same double-headed γ -camera (BrightView, Philips Healthcare, Best, The Netherlands). Whole body (WB) images (15 cm/min scan speed,

matrix size 1024×512, pixel size 2.80 mm) were performed immediately following administration, at 1, 4–6 and 24 hours postinjection. A standard activity of ~5 MBq Tc99m in an unshielded syringe was always in the field of view for quantification purposes. Static images (5 min, matrix size 256×256, pixel size 2.33 mm) of hands and feet were acquired immediately following the first WB scan which was started within a couple of minutes postinjection, at 4–6 and 24 hours postinjection. A single photon emission tomography (SPECT) was acquired from the axial skeleton. In selected cases, a SPECT/CT was performed to depict in detail the involved joints.

To assess the tracer accumulation in the peripheral joints, each joint was scored semiquantitatively by using the following scoring system: score 0=no tracer uptake, score 1=faint uptake of the tracer and score 2=clear uptake of the tracer. The same score was applied to every quadrant of the SIJs in patients with axSpA. The scintigraphic result was defined as positive if there was faint or clear tracer uptake 4–6 hours postinjection. As the scintigraphic images do not provide anatomic details, fusion of the MRI with the nuclear image was performed to allow scoring of the tracer uptake per quadrant. For each individual scan, a background region of interest (ROI) was defined within the field of view, for example, left supraclavicular region on WB, right forearm on static images of the wrists and hands, and right distal tibia for the static images depicting the ankles and feet. These results were compared with the findings from clinical examination of each assessable joint. The nuclear medicine physician reading the immunoscans, and the clinician performing the clinical examination were blinded to each other's observations.

Statistical analysis

Data were analysed using SAS V.9.3 (SAS Institute Inc, Cary, North Carolina, USA). Both a joint-based and patient-based analysis were done. In the joint-based analysis, each individual joint contributes an observation, but clustering of the joints within the patient was taken into account in the statistical analysis. For this analysis a scintigraphic score corresponding to either faint or clear tracer uptake 4–6 hours postinjection was considered as positive. To determine the relationship between the scintigraphic variable and the (clinical or US) status of the joint at baseline, a mixed logistic regression model with patient as random effect was used. For the predictive value of the scintigraphic variable on the status of the joint 12 and 24 weeks after treatment, the data set is reduced to only those joints that were tender and/or swollen at baseline according to the variable assessed in the analysis. A mixed logistic regression model with patient as random effect is used on this reduced data set. The results of the logistic regression model are summarised in terms of the OR and percentage of tender and/or swollen joints in the positive and negative scintigraphic group. In the patient-based analysis summary

statistics at the patient level was used. In this analysis the sum of the semiquantitative scintigraphic scores was used: for patients with RA, the scores of wrists, MCP and proximal interphalangeal joint (PIP) joints were used whereas in pSpA, the scores of the hand distal interphalangeal joint (DIP) joints were added; in patients with axSpA, the sum scores of the quadrants of the SIJs was used. To assess the predictive value of the scintigraphic variable at baseline on the clinical improvement at 12 and 24 weeks after treatment (measured by ASDAS for patients with axSpA and pSpA; measured by DAS28 for patients with RA), a linear regression model is used with the scintigraphic scores included as a continuous variable. The results are summarised in terms of the slope. The slope describes the change in the respective clinical score with a unit increase in the scintigraphic variable. For all analyses $p < 0.05$ was considered statistically significant.

RESULTS

Patients baseline and disease characteristics and clinical response after 12 and 24 weeks treatment with CZP

Table 1 depicts the baseline characteristics and the clinical response after 12 and 24 weeks of treatment with CZP. The mean age±SD of patients with RA, pSpA and axSpA at baseline was 56.2±10.1, 41.0±10.3 and 37.1±10.7 years with a mean symptom duration of 13.1±15, 12.6±14.9 and 9±6.7 years, respectively. The mean CRP level at baseline for patients with RA, pSpA and axSpA was 10.9, 15.4 and 4.7 mg/L, respectively. In general, there was a clear improvement of signs and symptoms in all patients treated with CZP. Three of the five patients with RA had a good EULAR DAS28 response, and two had a moderate EULAR DAS28 response after 12 weeks treatment. At 24 weeks, loss of response was observed in one patient with RA. Three of the six patients with pSpA showed a major ASDAS improvement after 12 weeks treatment while two had a clinically important ASDAS improvement. One patient with pSpA was a (primary) non-responder, and one patient with pSpA lost response after 24 weeks treatment. In the patients with axSpA group, two out of nine had a major ASDAS response, and six patients had a clinically important ASDAS response. Again, one patient with axSpA was a primary non-responder and one patient with axSpA lost response at 24 weeks treatment. The scintigraphic procedure was well tolerated. No procedure-related adverse events were observed.

Description of distinct scintigraphic patterns observed in patients with RA and SpA

In most of the clinically involved joints of hands and feet in patients with RA and pSpA, a tracer uptake was immediately visualised within minutes following the injection, probably due to vascular hyperaemia. At 4–6 hours postinjection, more joints were showing an enhanced uptake, with the more favourable joint-to-background ratio allowing a good anatomical

Table 1 The baseline characteristics of all patients and their clinical response after 12 and 24 weeks treatment with CZP

Baseline characteristics																	
Demographic characteristics		Disease characteristics								After 12 weeks CZP				After 24 weeks CZP			
		Symptom duration (years)	Concomitant sDMARDs	Concomitant corticosteroids	Concomitant NSAIDs	CRP (mg/L)	ESR (mm/hour)	DAS 28	ASDAS	CRP (mg/L)	ESR (mm/hour)	DAS28	ASDAS	CRP (mg/L)	ESR (mm/hour)	DAS28	ASDAS
Age (years)	Gender (M/F)																
RA (n=5)																	
68.8	F	38.7	MTX 10 mg	Yes	No	32	23	6.77	–	1.5	4	1.93	–	0.8	4	1.76	–
62.1	F	3.1	MTX 10 mg	Yes	No	8.6	11	6.33	–	13.3	13	4.79	–	9.1	16	3.29	–
57.2	M	1.5	MTX 15 mg	Yes	No	9.5	24	5.8	–	0.6	4	4.31	–	0.7	6	4.86	–
42.8	F	11.6	MTX 12.5 mg	No	No	3.9	15	4.62	–	2	12	2.16	–	3.7	11	2.24	–
50.3	F	10.8	No	Yes	No	0.6	8	3.89	–	0.6	10	2.31	–	0.6	10	3.87	–
pSpA (n=6)																	
45.9	M	17.3	MTX 15 mg	No	Yes	51.9	67	–	4.78	2.8	6	–	1.56	0.6	2	–	0.99
36.8	F	0.9	No	No	Yes	3.4	5	–	4.16	1.6	4	–	3.87	1.6	4	–	3.87
55.4	F	39.9	No	No	Yes	0.1	6	–	2.18	0.6	3	–	1.02	0.6	7	–	2.98
44.8	M	4.2	LEF	No	Yes	28.2	57	–	3.89	0.6	5	–	0.46	0.7	5	–	0.93
25.1	M	1.2	SSZ	No	Yes	3.5	6	–	3.64	0.6	1	–	1.38	0.6	2	–	0.88
37.8	M	12.2	No	No	No	5.1	14	–	2.35	0.6	3	–	0.38	0.6	5	–	0.56
nraxSpA (n=5)																	
26.7	F	4.4	No	No	Yes	9	8	–	3.05	2.7	3	–	1.65	0.7	2	–	1.61
42.4	M	5.2	No	No	Yes	2.5	5	–	2.94	0.7	2	–	2.22	0.6	1	–	2.91
45.8	M	19	No	No	Yes	4	11	–	2.67	0.6	3	–	0.73	0.6	3	–	0.68
44.5	M	3.5	No	No	Yes	6.3	4	–	3.38	3.9	5	–	1.58	4.2	7	–	3.25
35.2	F	19	No	No	Yes	4	5	–	4.07	6.2	8	–	2.59	5.7	11	–	2.18
AS (n=4)																	
29.2	M	4.6	No	No	Yes	8	15	–	4.27	4.1	8	–	1.66	1.3	1	–	1.14
27.2	M	12.3	No	No	Yes	1.1	1	–	3.28	4.2	2	–	1.32	0.6	2	–	0.63
26.3	M	1.6	No	No	Yes	3	4	–	2.31	0.6	2	–	0.63	0.6	2	–	0.44
56.4	M	11.4	No	No	Yes	4.6	6	–	3.4	1.3	2	–	1.2	2.1	5	–	1.52

axSpA, axial spondyloarthritis; AS, ankylosing spondylitis; ASDAS, Ankylosing Spondylitis Disease Activity Score; CRP, C reactive protein; CZP, certolizumab pegol; DAS28, Disease Activity Score in 28 joints; ESR, erythrocyte sedimentation rate; LEF, leflunomide; M/F, male/female; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; pSpA, peripheral spondyloarthritis; RA, rheumatoid arthritis; sDMARDs, synthetic disease-modifying antirheumatic drugs; SSZ, sulfasalazine.

discrimination of the various joints. In most joints, the tracer accumulation persisted over time on the 24-hour postinjection images. A typical polyarticular pattern of hand and feet joints without DIP involvement was seen in RA (figure 1A). In contrast, there was clear DIP involvement seen in the hands of a patient with polyarticular psoriatic arthritis (figure 1B). As a proof-of-concept, selected patients with pathognomonic clinical features were also scanned and in patients with pSpA with dactylitis, a specific scintigraphic pattern was observed with tracer uptake in the joints and the accompanying flexor tendon of the clinically involved digit of the hand or foot (figure 1C). Clear tracer uptake was also noticed at the enthesis of Achilles tendon and plantar fascia in patients with SpA with clinical and US-confirmed enthesitis (figure 1D). Tracer uptake could also be detected in the region of the SIJs in patients with axSpA with active inflammatory lesions on MRI (figure 1E).

Relationship between scintigraphic results and status of peripheral joints and SIJs at baseline

Results of the joint-based analysis are presented in tables 2–4. First, using the clinical evaluation of all

peripheral joints in all patients as a reference, we compared the percentage of tender and/or swollen joints to the scintigraphic result at baseline (tables 2 and 3). The percentage clinically involved joints was significantly higher ($p<0.0001$) in the scintigraphy-positive as compared with the scintigraphy-negative joints. In patients with RA and pSpA, the baseline US GS and PD results were additionally compared with the scintigraphic result (table 4). Also, the percentage of GS-positive and PD-positive joints was significantly higher ($p<0.001$) in the scintigraphy-positive as compared with the scintigraphy-negative joints. Higher ORs were observed for the swollen joint count and PD-positive joints as compared with the tender joint count and GS-positive joints. Finally, in patients with axSpA, the percentage of SIJ quadrants showing BME on MRI was significantly higher ($p=0.001$) in the scintigraphy-positive as compared with the scintigraphy-negative joints (table 4). Maksymowych *et al*³² graded a lesion as deep on MRI if there is a homogeneous and unequivocal increase in signal extending over a depth of at least 1 cm from the articular surface; this type of lesion was observed in seven of the nine patients with axSpA and in five out of these seven patients with axSpA (71%), clear scintigraphic tracer uptake was

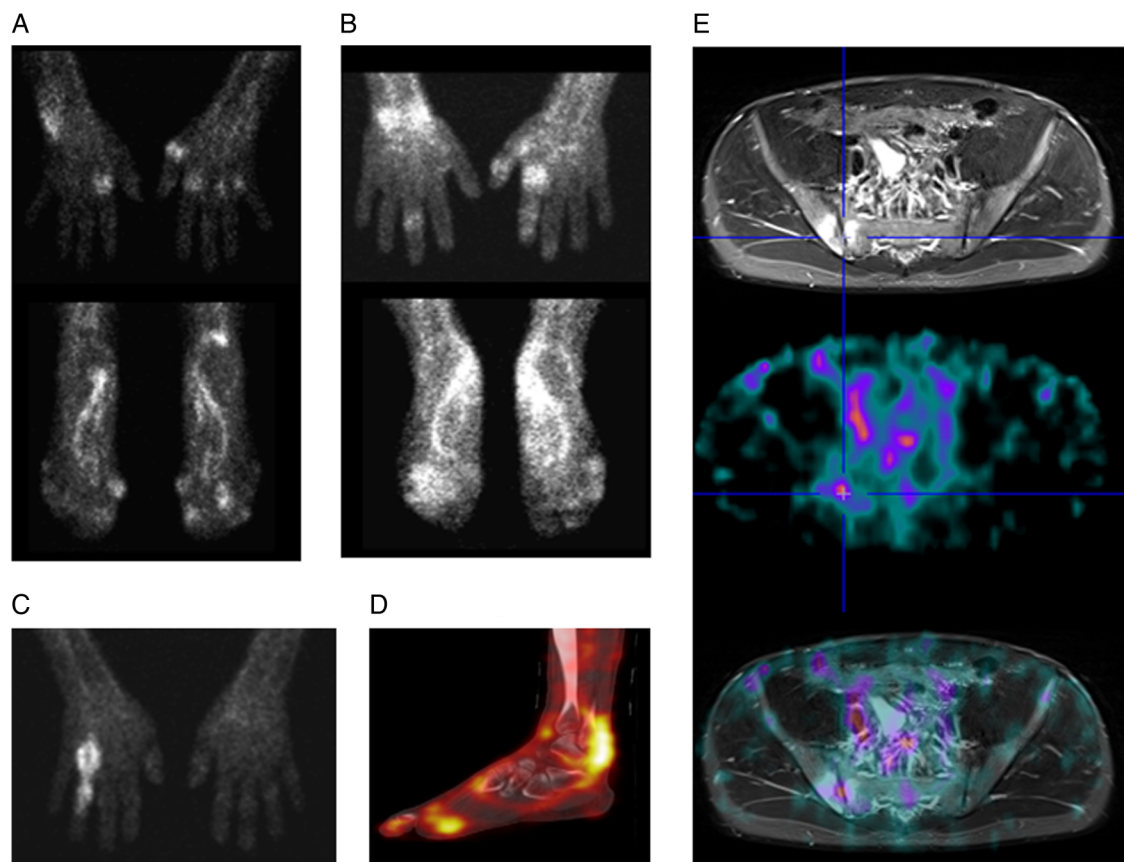


Figure 1 Distribution of Tc99m-radiolabelled certolizumab pegol in hands, feet and SIJs 4–5 hours postinjection. (A) A typical polyarticular pattern of hand and feet joints without distal interphalangeal joint (DIP) involvement was seen in a patient with active rheumatoid arthritis. (B) Distal interphalangeal joint uptake of the left second digit in a patient with polyarticular psoriatic arthritis. (C) Tracer uptake in both the joints and the accompanying flexor tendon in a patient with clinically dactylitis of the fourth digit at the right side. (D) SPECT-CT of the right foot in a patient with spondyloarthritis with enthesitis of the Achilles tendon. (E) Fusion of MRI and SPECT image of the sacroiliac joints of a patient with axial spondyloarthritis. SPECT, single photon emission tomography.

Table 2 The number and percentages of tender joints at baseline, and after 12 and 24 weeks of treatment as a function of the scintigraphic status at baseline

All patients	Scintigraphic negative			Scintigraphic positive			OR	p Value
	No tenderness	Tenderness		No tenderness	Tenderness			
Tender joints at baseline	1057 (91.8%)	95 (8.2%)		94 (56.3%)	73 (43.7%)		8.60	<0.001
		Not tender anymore at w12 or w24	Remains tender at w12 or w24		Not tender anymore at w12 or w24	Remains tender at w12 or w24		
Tender joints at w12		69 (72.6%)	26 (27.4%)		58 (79.5%)	15 (20.5%)	0.69	0.309
Tender joints at w24		65 (68.4%)	30 (31.6%)		64 (87.7%)	9 (12.3%)	0.30	0.004
w12, week 12; w24, week 24.								

w12, week 12; w24, week 24.

Table 3 The number and percentages of swollen joints at baseline, and after 12 and 24 weeks of treatment as a function of the scintigraphic status at baseline

Table 2. The number and percentages of swollen joints at baseline, and after w12 and w24 weeks of treatment, as a function of the scintigraphic status at baseline								
All patients	Scintigraphic negative			Scintigraphic positive			OR	p Value
	No swelling	Swelling		No swelling	Swelling			
Swollen joints at baseline	1059 (98.3%)	18 (1.7%)		104 (62.3%)	63 (37.7%)		36.85	<0.001
		Not swollen anymore at w12 or w24	Remains swollen at w12 or w24		Not swollen anymore at w12 or w24	Remains swollen at w12 or w24		
Swollen joints at w12		18	0		56 (88.9%)	7 (11.1%)	*	0.339
Swollen joints at w24		18	0		58 (92.1%)	5 (7.9%)	*	0.581

The OR refers to the odds of a joint being tender and/or swollen in the scintigraphic-positive as compared with the scintigraphic-negative group. For all tests, p values <0.05 are considered to indicate statistical significance.

*ORs for swollen joint count could not be estimated due to the fact that one cell, that is, scintigraphic-negative symptom has frequency zero.
w12, week 12; w24, week 24.

Table 4 The number and percentages of US grey scale and US power Doppler and MRI-positive joints at baseline as a function of the scintigraphic status at baseline

	Scintigraphic negative		Scintigraphic positive		OR	p Value
Patients with RA and pSpA						
US assessment	Normal US findings	Abnormal US findings	Normal US findings	Abnormal US findings		
US grey scale	192 (90.6%)	20 (9.4%)	28 (37.8%)	46 (62.2%)	15.77	<0.001
US power Doppler	207 (97.6%)	5 (2.4%)	33 (44.6%)	41 (55.4%)	51.44	<0.001
Patients with axSpA						
MRI assessments SIJs	No BME	BME	No BME	BME		
BME per quadrant	34 (70.8%)	14 (29.2%)	7 (21.9%)	25 (78.1%)	8.67	<0.001

The OR refers to the odds of a joint being US grey scale and US power Doppler positive or MRI positive in the scintigraphic-positive as compared with the scintigraphic-negative group. For all tests, p values <0.05 are considered to indicate statistical significance.
axSpA, axial spondyloarthritis; pSpA, peripheral spondyloarthritis; RA, rheumatoid arthritis; SIJs, sacroiliac joints; US, ultrasound.

observed in the same quadrant of the SIJs, where the extended lesion was also located. Interestingly, in one patient with AS with complete fusion of the SIJs (bilateral grade 4 sacroiliitis on X-ray), who was suffering from peripheral arthritis (and hence was included in the pSpA part of the study), there was an absence of BME of the SIJs on MRI. In this patient we could also not detect tracer uptake on scintigraphy. Although this is only a solitary case, it might suggest that in vivo detection of TNF correlates with active inflammatory lesions on MRI and not with structural damage.

Relation scintigraphic results and status of the patient at baseline

On a patient level, a linear regression model was fitted regressing the sum of the semiquantitative scintigraphic scores on patient-reported outcomes (SF-36, PGA of disease activity, PGA of pain) and relevant disease activity scores (DAS28 for RA, ASDAS for SpA). No significant linear relationship was found between the scintigraphic sum score and patient-reported outcomes or disease activity scores at baseline. Nevertheless, we found a significant relationship between the scintigraphic sum score of the SIJs and the SPARCC score ($p=0.010$). Each unit increase in the SPARCC score corresponds to an increase of 0.4139 (SE=0.119) in the scintigraphic sum score (figure 2).

Prediction of therapy response by scintigraphic result on joint and patient level at weeks 12 and 24

Finally, the scintigraphic result was analysed as a potential predictor of therapy response of the joint level and patient level. At the joint level, we observed a significant result for

the number of tender joints at week 24 (table 2): of all tender joints that were positive on scintigraphy at baseline, only 11.9% remained painful at week 24, compared with 26.5% in the scintigraphy-negative joints (OR=0.38; $p=0.030$). Results for swollen joints are summarised in table 3; no significant correlation was found.

At the patient level, a linear regression model was fitted regressing the sum of the semiquantitative scintigraphic scores on the change in patient-reported outcomes (SF-36, PGA of disease activity, PGA of pain), physician global assessment and relevant disease activity scores by inserting group as adjusting factor in the model. For patients with RA, the difference in DAS28 between baseline and weeks 12 and 24 was used and regressed on the scintigraphic sum score. For patients with SpA, the difference in ASDAS between baseline and weeks 12 and 24 was used and regressed on the scintigraphic sum score. No significant relationships were found.

DISCUSSION

We performed a proof-of-concept study on patients with RA and SpA to detect in vivo TNF- α -driven inflammation by scintigraphy using radiolabelled CZP. We visualised in most of the clinically involved joints a marked tracer uptake within minutes following injection, suggesting fast uptake into the inflamed tissue. The best results were seen at 4–6 hours postinjection, but tracer uptake was still observed on the 24 hours postinjection scan, suggesting that uptake is not solely caused by a vascularisation effect. We were able to visualise specific tracer uptake patterns pathognomonic for the studied diseases. Although similar results have been reported with

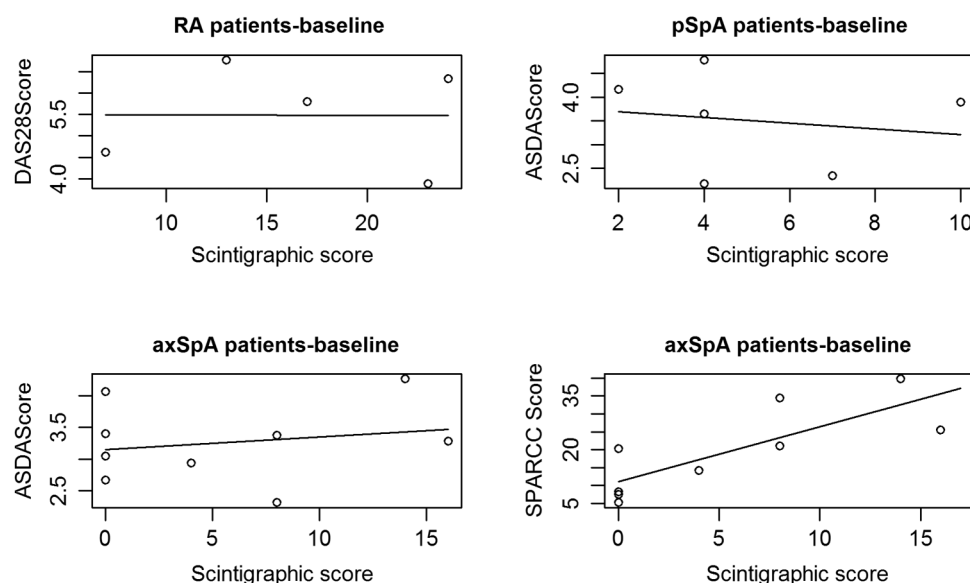


Figure 2 Relationships between the baseline disease activity scores and scintigraphic sum scores for the patients with RA, pSpA and axSpA. ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; DAS28, Disease Activity Score in 28 joints; pSpA, peripheral spondyloarthritis; RA, rheumatoid arthritis; SPARCC, the Spondyloarthritis Research Consortium of Canada scoring system.

radiolabelled adalimumab in patients with RA,^{33 34} this is—to the best of our knowledge—the first study to evaluate immunoscintigraphic patterns in patients with different subtypes of SpA by visualising enthesitis, dactylitis and sacroiliitis.

Second, in patients with peripheral joint involvement, we could establish a good correlation between the clinical evaluation and conventional imaging of the individual joints, and the tracer uptake on scintigraphy. Interestingly, this correlation was strongest for more objective signs of inflammation: higher ORs were observed for the swollen joint count and PD-positive joints as compared with the tender joint count and GS-positive joints. At the patient level, no significant correlation was found between the scintigraphic sum score and global disease activity scores or relevant patient-reported outcomes. In patients with axSpA, the scintigraphic findings correlated well with BME on MRI of the SIJs, which is the item that is required in the ASAS definition of a positive MRI,³⁵ and is one of the anchors of the ASAS classification criteria for axSpA. Nevertheless, the interpretation of a ‘positive MRI’ in the context of SpA remains difficult, definitely when the presence of BME is subtle or when there may be other causes for the observed BME, such as mechanical stress. As a consequence, there is still an unmet need to determine whether observed BME is caused by underlying cytokine-driven inflammation in patients with axSpA. At present, there is no agreement on a precise definition of the minimum size (area) of BME which is necessary to be defined as ‘positive’. There is an impression that the presence of so-called ‘deep’ BME lesions on MRI of the SIJs, defined as a homogeneous and unequivocal increase in signal extending over at least 1 cm from the articular surface on STIR images, would be more suggestive of axSpA. In our study, taking only these extended lesions on MRI of the SIJs into account, better correlations between scintigraphy and MRI were found. Finally, at the patient level, there was a significant relation between the scintigraphic sum score of the SIJs and the SPARCC scoring system.

Third, we looked whether the baseline scintigraphic detection of TNF could predict a therapeutic response to CZP therapy after 12–24 weeks. We need to emphasise that this study was not designed or powered to predict therapy response by baseline scintigraphic results. Nevertheless, we could demonstrate a significant predictive value of the immunoscintigraphy at the joint level with regard to the tender joint count: tender joints with uptake at baseline had a significantly higher probability of not being painful after 24 weeks of treatment. The lack of predictive value for the other joint assessments, as well as for the global disease activity scores at the patient level, could probably be explained by the fact that the study included only small numbers of patients with heterogeneous inflammatory diseases. These preliminary findings are, however, interesting because a positive scintigraphic result might indicate that joint

tenderness at baseline is TNF-driven, and this result could serve as a more objective measurement tool for tender joints. Surprisingly, only two prospective cohort studies in RA have assessed the use of imaging techniques to predict response to anti-TNF therapy. Ellegaard and colleagues measured US Doppler activity and clinical parameters at baseline to predict which patients would benefit from treatment, assessed by treatment persistence at 1 year. They identified US Doppler activity to be the only baseline parameter able to predict treatment persistence ($p=0.024$); baseline clinical measures, including tender and swollen joint counts, CRP, DAS28, and HAQ showed no significant association.³⁶ Elzinga and colleagues used changes in positron emission tomography (PET) uptake 2 weeks after treatment to predict future treatment response, according to DAS28. A significant correlation was seen between the changes in PET activity at 2 weeks, and DAS28 at 14 and 22 weeks after treatment ($r\ 0.62$, $p<0.05$; $r\ 0.65$, $p<0.01$, respectively).³⁷

In the past, only few attempts in molecular imaging using radiolabelled monoclonal antibodies in rheumatic diseases were made, and the earliest experiences and clinical context are excellently summarised by Malviya *et al.*³⁸ Our study is the first using a radiolabelling procedure with CZP, a PEGylated Fab fragment directed against TNF- α . One of the reasons for choosing CZP as a tracer was the observation made in an animal model for arthritis using biofluorescence imaging: a greater ratio of penetration and more prolonged duration of exposure in inflamed versus normal tissue was described for CZP compared with adalimumab and infliximab. One possible explanation could be the link with PEG in CZP.³⁹

We acknowledge that our study has several limitations, both regarding the scintigraphic technique, as well as concerning the type of patients that was studied. Barrera *et al.*³³ published encouraging findings with radiolabelled adalimumab in 10 patients with active RA. A subset of patients underwent repeat imaging following administration of a therapeutic dose of cold antibody. Based on this competition study, the authors suggested a partial specific targeting of TNF- α by Tc99m-labelled adalimumab. These findings were in agreement with Roimicher *et al.*³⁴ We decided not to include a competition study and prioritised to first have an estimation of the radiation burden before exposing volunteering patients twice.⁴⁰ We also did not perform a second immunoscintigraphy after 12 or 24 weeks of treatment in order to evaluate the change in tracer uptake over time. We first wanted to establish a proof-of-concept with this new radiopharmaceutical before endorsing more complex follow-up scintigraphic procedures. Nevertheless, it was Conti *et al.*⁴¹ who showed a positive predictive role of 99mTc-infliximab scintigraphy in therapy decision-making for patients with refractory monoarthritis who were given intra-articular infliximab treatment by comparing the pretherapy and post-therapy target-to-background ratio from affected joints.

With regard to patient selection, this was obviously a proof-of-concept study, which included only limited numbers of patients with different inflammatory rheumatic diseases. We did not include a non-inflammatory control group; as a consequence, we cannot exclude that the observed tracer uptake could be an aspecific phenomenon, although the good correlation with the clinical evaluation and conventional imaging results would argue against this. The low number of patients in each disease subgroup evidently does not allow us to make conclusions regarding prediction of clinical response in case of a positive scintigraphy; nevertheless, the finding that individual painful joints that were scintigraphy-positive had a higher odds of becoming not tender after treatment with certolizumab could be a promising find. Indeed, since treat-to-target principles have found their way in the daily management of patients with RA,⁴² a high number of tender joints might be one of the triggers to change the therapeutic strategy: information as to whether the observed pain pattern is related to in vivo expression of a culprit cytokine could potentially avoid overtreatment with biologicals in individual cases where pain is driven by other pathophysiological mechanisms.

CONCLUSION

In conclusion, we demonstrated that it is safe and feasible to perform scintigraphy with radiolabelled CZP in patients with different types of inflammatory arthritis, whereby specific joint involvement patterns could be recognised. Future research should confirm these preliminary results, specifically with regard to the potential to predict clinical response to a biological treatment targeting TNF. If confirmed, the technique could be a step towards personalised medicine, where each patient receives the right drug and the right intensity of treatment for as long as needed; it could allow the selection of patients for a specific therapy in a much more rational way than the current 'trial and error' approach. In particular, future studies should address if a pretherapy scintigraphic approach with a radiopharmaceutical targeting TNF identifies the presence of the target cytokine in the inflammatory lesion and if positive, whether these patients with clear uptake of the anti-TNF tracer would respond better to anti-TNF therapy as compared with strategies targeting other inflammatory pathways. This might be a crucial step in enhancing the safe and cost-effective use of expensive biological treatment by avoiding exposure of non-responders to treatments such as anti-TNF therapy.

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Scintigraphic detection of TNF-driven inflammation by radiolabelled certolizumab pegol in patients with rheumatoid arthritis and spondyloarthritis

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